REMARKS

Claims 1 and 3-8 stand rejected. Applicants have herein amended claim 1 to recite that the transgenic mouse exhibits elevated levels of IgM, IgG1, IgG2b, IgA, and IgE isotypes as compared with a corresponding wild-type mouse, that the transgenic mouse is capable of surviving at least 60 days, and that a serum sample from the transgenic mouse does not exhibit a clonal spike of gamma immunoglobulin. Support for these amendments can be found in the specification at, for example, page 4, lines 8-10; page 14, line 31, to page 15, line 4; and in Figure 3A. New claims 30-32 also have been added herein. Support for claims 30-32 can be found in the specification at, for example, page 15, line 31, to page 16, line 18. Thus, no new matter has been added.

Upon entry of the amendments herein, claims 1, 3-8, and 30-32 will be pending and under examination. In light of the above amendments and the following remarks, Applicants respectfully request reconsideration and allowance of claims 1, 3-8, and 30-32.

Rejections under 35 U.S.C. § 103

The Examiner maintained the rejection of claims 1 and 3-7 under 35 U.S.C. § 103(a), alleging that they are unpatentable over the Grillot et al. reference [(1996) J. *Exp. Med.* 183:381-391; "Grillot"], in view of the Adams et al. reference [(1985) *Nature* 318:533-538; "Adams"]. The Examiner asserted that Adams demonstrated that both the heavy chain and kappa chain enhancers effectively drive B cell specific heterologous transgene expression in transgenic mice, and that the rationale for combining the references is "simple substitution of one known element for another to obtain predictable results." Office Action at page 5.

The Examiner also maintained the rejection of claim 8 under 35 U.S.C. § 103(a), alleging that it is unpatentable over the Grillot et al. reference in view of the Adams et al. reference as applied to claims 1-7 above, and further in view of the Miller et al. reference [(1992) *Immunogenetics* 35:24-32; "Miller"].

Applicants respectfully disagree with respect to the present claims. Obviousness under § 103 requires consideration of the factors set forth in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966), including an analysis of the scope and content of the prior art and the

differences between the claimed subject matter and the prior art. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007). Without acquiescing to the Examiner's rejection, and to further prosecution, Applicants have amended claim 1 herein to recite that the transgenic mouse exhibits elevated serum levels of IgM, IgG1, IgG2b, IgA, and IgE isotypes as compared with a corresponding wild-type mouse. Claim 1 has been further amended to require that the transgenic mouse be capable of surviving at least 60 days, and that a serum sample from the transgenic mouse does not exhibit a clonal spike of gamma immunoglobulin.

The cited combinations of references do not render the present claims obvious. Neither Grillot nor Adams teaches or suggests transgenic mice where the transgene comprises an immunoglobulin kappa light chain 3' enhancer sequence operably linked to a nucleic acid sequence encoding an anti-apoptotic polypeptide in the Bcl-2 family. Nor do the references teach or suggest transgenic mice having the required properties of expanded plasma cell and mature B cell populations, elevated serum levels of IgM, IgG1, IgG2b, IgA, and IgE isotypes, capability to survive to at least 60 days, and absence of a clonal spike of serum gamma immunoglobulin. A person of ordinary skill in the art at the time of filing would not have been prompted by Grillot or Adams to use the immunoglobulin kappa light chain 3' enhancer to obtain transgenic mice having these specific properties.

Applicants also respectfully submit that, as argued previously, Adams effectively teaches away from substituting the kappa enhancer for the heavy chain enhancer when the goal is promoting tumor growth. The heavy chain enhancer-myc construct resulted in higher tumor incidence than observed with the light chain enhancer-myc construct, suggesting that the heavy chain enhancer has greater activity than the light chain enhancer, at least with certain promoters, or has a larger pool of susceptible cells. Thus, a person of ordinary skill in the art reading Adams at the time of Applicants' priority date would not have been prompted to make the "simple substitution" alleged by the Examiner.

Further, with respect to claim 8, Applicants showed that combining the Ig promoter with the Ig 3' kappa enhancer provided specificity and higher expression. This had not been tested by others as of Applicants' priority date. Indeed, oncogenic transformation of plasma cells did not occur unless the Ig promoter and the Ig 3' kappa enhancer were paired with the anti-apoptotic Bcl-xL construct developed by the inventors. As described in Applicants' specification, Bcl-xL

expression significantly increased the number of plasma cells in the mice, significantly increased antibody production, and elevated serum levels of Ig isotypes without adverse effects on animal survival. See, for example, the specification at page 14, line 31, to page 15, line 4; page 15, lines 14-17; and page 16, lines 5-29. Thus, Applicants' constructs combining the Ig promoter with the Ig 3' kappa enhancer have unique properties that allow for plasma cell expression not found in other pairings.

For at least these reasons, a person of ordinary skill in the art reading either the combination of Grillot in view of Adams, or the combination of Grillot in view of Adams and further in view of Miller, would not have been prompted to make a transgenic mouse as recited in the present claims. As such, the claims are patentable over these combinations of references.

In light of the above, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 103(a).

CONCLUSION

Applicants submit that claims 1, 3-8, and 30-32 are in condition for allowance, which action is respectfully requested. The Examiner is invited to telephone the undersigned if such would further prosecution.

Please apply any charges or credits to deposit account 06-1050, referencing Attorney Docket No. 09531-0109US1.

Respectfully submitted,

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